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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,804	WILLIAMSON ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-106,109 and 111-114* is/are pending in the application.

4a) Of the above claim(s) *76-105 and 112-114* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106, 109 and 111* is/are rejected.

7)☒ Claim(s) *111* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 22, 2009 has been entered.

2. Claim 106 has been amended.

3. Claims 106, 109 and 111 are currently under consideration as drawn to the species mutation site 5653 of the plexinB1 coding sequence and the A5653G mutation.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 106, 109, and 111 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention essentially for the reasons set forth in the Office Action of October 27, 2008, section 3, pages 2-3.

Examiner argued:

Claim 107 refers to one or more mutation in a region of the nucleic acid which encodes, the cytoplasmic domain of the plexinB1 polypeptide, Claim 108 refers to one or more mutations at site 5653 of the plexinB1 coding sequence and claim 109 refers to the mutation A5653G. However, given that there is no point of reference given as to where the cytoplasmic domain of plexinB1 begins or ends and there is no point of reference given as to where the mutations of

claim 108 and 109 are located, such as a SEQ ID NO: for plexinB1, the claims are indefinite as it cannot be determined to where these mutations are located.

Applicants argue that they believe the amendments will obviate this rejection.

Applicants' arguments have been considered, but have not been found persuasive because the mutations of claim 106 encompasses the mutations of claim 109 and the mutations of claim 109 are not limited to SEQ ID NO: 112. Furthermore, SEQ ID NO: 112 is not AB0007867.1, but AB007867.1, see Appendix 1. Thus, it cannot be determined to which coding sequence the claims are drawn SEQ ID NO: 112 or AB0007867.1. Given its broadest reasonable interpretation the claim is drawn to SEQ ID NO: 112 or AB0007867.1 and the location of the mutations in AB0007867.1 is indefinite for the reasons previously set forth.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 106, 109 and 111 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in section 4, pages 3-10 of the Office Action of October 27, 2008.

Examiner argued:

One cannot extrapolate the teachings of the specification to the enablement of the claims because one of skill in the art would not be predictably able use changes in either the wild type plexinB1 or the A5653G mutant to identify or obtain a putative anti-cancer agent. Although the A5653G mutation is found in primary and metastatic prostate tumors, this same mutant plexinB1 reduces the tumorigenicity of cells *in vivo*. Thus, it is not clear if this mutation is a positive or negative regulator of prostate tumor or any tumor formation as the mutation appears to be associated with both positive and negative regulation of tumor formation and one of skill in the art would not predictably know what change in expression of the A5653G mutant B1 nucleic acid would be important for affecting tumor formation and would not predictably be able to identify and/or obtain a compound as a putative anti-cancer agent based on change in expression

of the A5653G mutant plexinB1. Thus, undue experimentation would be required for identifying and/or obtaining a putative anti-cancer agent by the claimed method.

Additionally, it is not predictable that determining an increase in the wild-type plexinB1 would lead to the identification of a putative anti-cancer agent. Although the specification teaches that the expression of the wild-type plexin B1 suppresses tumor formation, Mack and Gish (US Pat. App. Pub. 2004/0005563, June 17, 2002) teach that plexin B1 is upregulated in ovarian cancer, see Table 14A and para. 0348 of the published application and Vogelstein et al. (US Pat. App. Pub 2005/0047996, October 9, 2001) teach that plexin B1 is upregulated in colorectal cancer, see Table 1. Thus, given that plexin B1 is upregulated in ovarian and colorectal cancers, the determination of an increase in the wild-type plexin B1 by a test compound would not predictably identify a putative anti-cancer agent. Thus, undue experimentation would be required for identifying and/or obtaining a putative anti-cancer agent by the claimed method.

Furthermore, given that A5653G mutant plexin B1 has only be identified in prostate cancers, one of skill in the art would not predictable expect that agents that affect the expression of this mutant plexinB1 nucleic acid would be putative anti-cancer agents for any cancer because it is well known in the art that cancers are heterogeneous in phenotype and genes expressed and cancer therapeutics are not predictably effective for all cancers.

In particular, cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between the A5653G mutant plexin B1 and prostate cancer, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore, Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and there are no drugs broadly effective against all forms of cancer, see Carter, S. K. et a1. Chemotherapy of Cancer; Second edition; John Wiley & Sons : New York, 1981; appendix C. Given the above, it is clear that it is not possible to predictably

extrapolate any potential correlation between an A5653G mutant plexin B1 directed anti-cancer agents and prostate cancer sensitivity to such an agent in any tumor type based on the information in the specification and known in the art without undue experimentation.

Furthermore, one of skill in the art would not predictably expect that all of the broadly claimed mutants of plexinB1 to be associated with cancer and thus an effect on their expression would not predictably be useful for identifying a compound as a putative anti-cancer agent. It is noted that the specification teaches that a mutant plexinB1 nucleic acid may comprise a nucleotide sequence which has one or more mutations relative to the wild-type plexinB1 nucleotide sequence, as set out in AB007867. The mutations may be deletions, insertions or substitutions of one or more nucleotides see para. 0014 of the published application. Given the above and given that claims are drawn to contacting "a" plexin B1 nucleic acid, which reads on fragments, which comprises one or more mutations in a coding region of the nucleic acid, the broadest reasonable interpretation of the claims is that the claims are not limited to any specific plexinB1 mutants and the plexinB1 mutants can comprise nucleic acids that are completely distinct from plexinB1. Furthermore, given claims 108 and 109 are indefinite in lacking a point of reference, these claims are also not limited to a particular site of mutation within the coding region of the plexinB1 nucleic acid and the plexinB1 mutants can comprise nucleic acids that are completely distinct from plexinB1.

It would not be expected that such a diverse array of mutants of plexin B1 would predictably be associated with cancer given that even naturally occurring gene variants, such as splice variants, do predictably have the same expression pattern or encode proteins with the same function as the related variants.. In particular, Benedict et al (J. Exp. Medicine, 2001, 193(1) 89-99) specifically teach that two splice isoforms of terminal deoxynucleotide transferase (a long form and a short form) enter the nucleus but have different activity, the long form does not catalyze nontemplated nucleotide addition but rather modulates the activity of the short form (see abstract). Jiang et al (JBC, 2003, 278(7) 4763-4769) specifically teach that the type 3 Ca2+ release channel, RyR3 exhibits strikingly different pharmacologic and functional properties depending on the tissues in which it resides. Upon examination, seven tissue specific alternatively spliced variants of RyR3 were detected. One of the variants was unable to form a functional channel but was able to suppress the activity of a different release channel. The authors conclude that tissue-specific expression of RyR3 splice variants is likely to account for some of the pharmacologic and functional heterogeneities of RyR3 (see abstract). The abstract of Matsushita et al (FEBS Letters, 1999, Vol. 443, pp. 348-352) teaches that latrophilins exhibit alternative splicing resulting in latrophilin-1, which is present in brain and endocrine cells, latrophilin-2, which is ubiquitous, and latrophilin-3 which is brain-specific. The abstract of Singh et al (Glycobiology, 2001, Vol. 11, pp. 587-592) teaches that the CD44 splice variant, CD44v, is the major PNA-binding glycoprotein in colon cancer cells in contrast to standard CD44. These references serve to demonstrate that one of skill in the art cannot anticipate the biological activity of the proteins encoded by the broadly claimed plexinB1 mutants or the tissue distribution of the claimed mutants based on the biological activity of the protein encoded by the wild-type or tissue distribution of the wild-type nucleic acid or other mutants of plexinB1. Thus, even if it were found that the examination of the expression of the A5653G plexin B1 mutant could be used as

claimed, undue experimentation would be required to use the broadly claimed mutants or even other mutations at position 5653 for the identification of putative anti-cancer agents.

The specification provides insufficient guidance with regard to the issues set forth above and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Applicants argue that the Section 112, first paragraph "enablement", rejection of claims 106, 109 and 111 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments and the attached Wong et al ("Plexin-B1 mutations in prostrate cancer" PNAS November 27, 2007, vol. 104, no. 48, 19040-19045).

Applicants argue that the Examiner is understood to believe that the specification lacks experimental data which shows that the claimed mutations are involved in the etiology of cancer, so one of skill in the art could, according to the Examiner, not predictably use the claimed methods for identification of an anticancer drug without undue experimentation.

Applicants argue that the Examiner is requested to see the attached Wong et al, which is a peer- reviewed publication co-authored by the present inventors which contains the mutation data which is set out in the instant specification. Wong et al also contains additional data which shows the functional effects of four separate plexinB1 mutations (A5359G; A5653G; T5714C and C5060T) in cultured cells.

Applicants argue that all four plexinB1 mutants were shown to decrease the shrinkage or collapse of COS-7 cells relative to wild-type plexinB1 (Wong et al; figure 3c) and to significantly increase the adhesion of HEK293 cells relative to wild-type plexinB1 (Wong et al; figure 3d).

Applicants argue that furthermore, plexinB1 mutation was also shown to significantly increase the rate of migration of HEK293 cells relative to wild-type plexinB1 (Wong et al; figure 4a) and to increase the invasive capacity of HEK293 cells relative to wild-type plexinB1 (Wong et al; figure 4b). Expression of plexinB1 mutants in HEK293 cells was also shown to significantly increase the percentage of cell spreading and average cell size relative to expression of wild-type plexinB1 (Wong et al; figures 5a and 5b).

Applicants argue that in addition, mutation of plexinB1 is also shown to inhibit RacGTP and R-Ras binding (Wong et al; figures 5c, 6a and 6b), which may contribute to the observed increase in cell adhesion and motility (Wong et al; page 19044 col. 1 2nd para)

Applicants argue that the functional data set out in Wong et al provides further confirmation that plexinB1 mutation is functionally important in the etiology of cancer, and in particular cancer progression. For example, Wong et al states at page 19044 col. 1;

Together these results suggest that Plexin-B1 has a role in prostate cancer progression.

Applicants argue that Wong et al further state the following at page 19044 col. 2;

Plexin-B1 is likely to be a key player in cancer invasion and metastasis and is a potential target for anticancer therapy.

Applicants argue that it is therefore evident that plexinB1 mutations are involved in the etiology of cancer. The claimed methods could therefore be predictably used by one of ordinary skill in the art for identifying a compound as a putative anti-cancer agent.

Applicants' arguments have been considered, but have not been found persuasive because the functional studies of Wong et al. of the plexin B1 are based on *in vitro* studies in cell lines, which do not predictably extrapolate to *in vivo* anti-cancer activity. In particular, the

characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12: 320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the

acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-1802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al. further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). More recently, Zips et al (In vivo, 2005, 19:1-7) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col. 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col. 2).

Additionally Clark et al. (US Pat. App. Pub. 2006/0019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in de novo tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-population of cancer cells that are specifically adapted to growth in tissue culture and the

biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties in vivo. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of the original stem cells from which they were derived. Even when conditions are devised to permit the proliferation of normal stem cells in culture, the conditions often promote self-renewal or differentiation in a way that prevents the stem cells in culture from recapitulating the hierarchy of cell populations that exist in vivo. Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109.

Thus, given the above the *in vitro* cell culture data presented Wang et al. do not provide enabling support for the claimed method, in the absence of data that the 5653 mutations affect cancer growth *in vivo*, such as in animal model system. Furthermore, the teachings of Wang et al. are not commensurate in scope with the claimed method as the claimed method encompasses a much broader array of mutations than those examined by Wang et al. Thus, given the unpredictability in the art previously set forth and above, the rejection is maintained for the reasons previously set forth and above.

5. Claims 106, 109, and 111 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons set forth in the Office Action of October 27, 2008, section 5, page 10.

Examiner argued:

The limitation of a "the plexinB1 coding sequence of AB0007867.1" claimed in Claims 106, 109, and 111 has no clear support in the specification and the claims as originally filed. A review of the specification as revealed support for AB007867.1, see page 8, line 29. Thus subject matter claimed in Claims 106, 109, and 111 broadens the scope of the invention as originally disclosed in the specification.

Applicants argue that they believe the amendment will obviate this rejection.

Applicants' argument has been considered, but has not been found persuasive because claims are still drawn to "the plexinB1 coding sequence of AB0007867.1" and the specification only refers to AB007867.1, e.g. see page 6-line 4. Additionally, a review of the specification and claims as originally filed does not reveal support for SEQ ID NO: 112. Thus subject matter claimed in Claims 106, 109, and 111 broadens the scope of the invention as originally disclosed in the specification.

New Grounds of Rejection/Objection

Priority

6. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Examiner has established a priority date of 11/10/2005 for claims 106, 109, and 111 because the claims as currently constituted recite AB0007867.1 and SEQ ID NO: 112 and a review of the parent Applications does not reveal the claimed limitations. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Specification

7. The amendment filed December 24, 2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NO: 111 and SEQ ID NO: 112.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

8. Claim 111 is objected to because of the following informalities: The claim does not end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. Claims 106, 109, and 111 are rejected as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of identifying a compound as a putative anti-cancer agent, the method comprising; determining the expression of a plexinB1 nucleic acid in a cell or cell lysate in the presence of a test compound, wherein said plexinB1 nucleic acid comprises mutations in the coding region of the nucleic acid at position 5653 of the plexinB1 coding sequence of AB0007867.1 (SEQ ID NO: 112), and; wherein the cancer is prostate or breast cancer. When given the broadest reasonable interpretation, a plexinB1 nucleic acid encompasses any nucleic acid comprising a mutation of the sequence at position 5653 of AB0007867.1 or SEQ ID NO: 112, given that the specification teaches that a mutant plexinB1 nucleic acid may comprise a nucleotide sequence which has one or more mutations relative to the wild-type plexinB1 nucleotide sequence, as set out in AB007867 and the mutations may be deletions, insertions or substitutions of one or more nucleotides (see the paragraph bridging pages 3-4 of the specification as originally filed) and given that the coding sequence of AB0007867.1 is not defined and is not SEQ ID NO: 112, see Appendix 1. In other words the claims encompass any nucleic acid comprising a mutation of position 5653 (or any other of the claimed mutation sites) of AB0007867.1 or SEQ ID NO: 112 with AB0007867.1 being undefined and does not require the retention of any other plexinB1 sequences. Furthermore, dependent claim 109 is not even limited to having the mutation be from AB0007867.1 or SEQ ID NO: 112, the scope of which is encompassed by independent claim 106. Thus, the genus of plexinB1 nucleic acids which comprise one or more mutations is highly variable that varies significantly both in structure and function. The description of plexinB1 mutations (see Table 1

and 2) in the specification fails to adequately describe the genus of plexin B1 mutations because said genus tolerates members which differ significantly in both structure and function from the plexinB1 nucleic acid. One of skill in the art can reasonably conclude that applicant was not in possession of a genus of plexinB1 nucleic acids which comprise one or more mutations at the time the invention was filed. Because the genus of plexinB1 nucleic acids which comprise one or more mutations is not adequately described, the method claims relying on said genus are also not adequately described.

As it is drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated,

does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

In the instant case the genus of plexinB1 nucleic acids which comprise one or more mutations is so broad that it does not define the members that do or do not fall with the genus and it does not define any structural features commonly possessed by members of the genus that distinguish them from nucleic acids not encompassed by the genus.

In the remarks of July 11, 2008, Applicants argued that the claimed invention is described in the specification in a manner that one of ordinary skill will appreciate that the applicants were in possession of the claimed invention at the time the application was filed. The present claims relate to a sub-genus of plexin B1 nucleic acids which contain a mutation located at one of a number of specified positions in the coding sequence of plexinB1 identified by reference to the sequence of database entry AB0007867.1.

Applicants argued that that the description of plexinB1 mutations in the specification (e.g. Tables 1 and 2) adequately describes the claimed invention, since one example of a plexin B1 nucleic acid with a mutation at each position is disclosed. Furthermore, the applicants believe that since the mutations are located at specified sites in the plexinB1 sequence, the claimed invention does not include species which differ significantly in either structure or function from these examples.

Applicants argued that the sites of mutation within the plexin B1 nucleic acids are identified by reference to the plexin B1 sequence of database entry AB0007867.1, so the positions of these mutations within the plexin B1 sequence can be readily determined.

Applicants argued that the subject-matter of the present claims is therefore described in the specification such a way as to reasonably convey to one skilled in the relevant art that the inventors has possession of the claimed invention at the time the application was filed.

Applicants' arguments have been considered, but have not been found persuasive because the claims are not limited to plexinB1mutants of AB0007867.1 or SEQ ID NO: 12. The claims encompass a plexin B1 nucleic acid that comprise mutations in the coding region that comprise a single nucleic acid mutation at position 5653 (or any of the other claimed mutation sites) of AB0007867.1 or SEQ ID NO: 12 . Furthermore, dependent claim 109 is not even limited to having the mutation be from AB0007867.1 (which is not defined) or SEQ ID NO: 112, the scope of which is encompassed by independent claim 106. Thus, the claims encompass nucleic acids that comprise no sequences related to AB0007867.1 or SEQ ID NO: 12. Thus, the description of a single plexinB1 and its mutations in the specification, fails to adequately describe this vast genus of nucleic acids.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 106, 109, and 111 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/068579 A2 (Venter et al. 6 September 2002).

The claims are drawn to:

106. A method of identifying a compound as a putative anti-cancer agent, the method comprising; determining the expression of a plexinB1 nucleic acid in a cell or cell lysate in the presence of a test compound, wherein said plexinB1 nucleic acid comprises mutations in the coding region of the nucleic acid at position 5653 of the plexinB1 coding sequence of AB0007867.1 (SEQ ID NO: 112), and; wherein the cancer is prostate or breast cancer.

109. A method according to claim 106, wherein the one or more mutations is A5653G.

111. A method according to claim 106, comprising determining a decrease in the expression of mutant plexin B1 in the presence of said test compound.

When given the broadest reasonable interpretation, a plexinB1 nucleic acid encompasses any nucleic acid comprising a mutation of the sequence at position 5653 of AB0007867.1 or SEQ ID NO: 112, given that the specification teaches that a mutant plexinB1 nucleic acid may comprise a nucleotide sequence which has one or more mutations relative to the wild-type plexinB1 nucleotide sequence, as set out in AB007867 and the mutations may be deletions, insertions or substitutions of one or more nucleotides (see the paragraph bridging pages 3-4 of the specification as originally filed) and given that the coding sequence of AB0007867.1 is not defined and is not SEQ ID NO: 112, see Appendix 1 . In other words the claims encompass any nucleic acid comprising a mutation of position 5653 (or any other of the claimed mutation sites) of AB0007867.1 or SEQ ID NO: 112 with AB0007867.1 being undefined and does not require the retention of any other plexinB1 sequences. Furthermore, dependent claim 109 is not even

limited to having the mutation from AB0007867.1 or SEQ ID NO: 112, the scope of which is encompassed by independent claim 106 and thus the A to G mutation could be anywhere in the mutant sequence.

It is noted that the recitation of "a method of identifying a compound as a putative anti-cancer agent . . . wherein the cancer is prostate or breast cancer" in claim 106 is merely suggestive of an intended use that does not result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art and thus is not given weight for comparison of the claims with the prior art.

WO 02/068579 teaches a plexinB1 sequence that is mutated relative to SEQ ID NO: 12 with a mutation at position 5653 and contains A to G mutations relative to SEQ ID NO: 12, see position 5579 for example, see Appendix 2. WO 02/068579 teaches determining the expression of the transcripts of the invention in cells in the presence of compounds in drug development and determining decreases in the expression of the transcripts in cells in the presence of the compounds under development, see page 30.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642

Appendix 1

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AB007867
LOCUS       AB007867               7308 bp    mRNA    linear   PRI 10-JAN-2004
DEFINITION  Homo sapiens KIAA0407 mRNA, partial cds.
ACCESSION   AB007867
VERSION     AB007867.1  GI:2662094
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Ishikawa,K., Nagase,T., Nakajima,D., Seki,N., Ohira,M.,
            Miyajima,N., Tanaka,A., Kotani,H., Nomura,N. and Ohara,O.
  TITLE     Prediction of the coding sequences of unidentified human genes.
            VIII. 78 new cDNA clones from brain which code for large proteins
            in vitro
  JOURNAL   DNA Res. 4 (5), 307-313 (1997)
   PUBMED   9455477
REFERENCE   2  (bases 1 to 7308)
  AUTHORS   Ohara,O.
  TITLE     Direct Submission
  JOURNAL   Submitted (06-OCT-1997) Osamu Ohara, Kazusa DNA Research Institute,
            Laboratory of DNA Technology; Yana 1532-3, Kisarazu, Chiba
            292-0812, Japan (E-mail:cdnainfo@kazusa.or.jp, Tel:+81-438-52-3913,
            Fax:+81-438-52-3914)
FEATURES             Location/Qualifiers
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                     /sex="male"
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     CDS             <247. .6678
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                     VGLVAQGLAGEPLLFVGRGYTSRGVGGGIPPITTRALWPPDPQAAFSYEETAKLAVGR
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AAAVENKVTDL"

ORIGIN

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  Query Match             100.0%;  Score 7308;  DB 5;  Length 7308;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches 7308;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

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Qy       2101 GAGCTCAGATTTGGCGCTGTTGTGATCGCCAAAACTTCCCTCTCTTTCTATGACTGTGTG 2160
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Qy       2161 GCGGTCACTGAACTCCGCCCATCTGCGCAGTGCCAGGCCTGTGTGAGCAGCCGCTGGGGG 2220
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Qy       2461 TCCCTGCTCAGCCCCTGGGGGCCATGGGCAGGTTCTGGCTCCATATCTTCCCCTGGCTCC 2520
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              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2641 CCGCTGTCACCGTCAGAGGTAGCAGCAGTGCCCCCTGCAGACCCTGGCCCCGAGGCTCTT 2700

Qy       2701 CATCCCACAGTGCCCCTGGACCTGCCCCCTGCCACTGTTCCTGCCACCACTTTCCCAGGG 2760
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2701 CATCCCACAGTGCCCCTGGACCTGCCCCCTGCCACTGTTCCTGCCACCACTTTCCCAGGG 2760

Qy       2761 GCCATGGGCTCCGTGAAGCCCGCCCTGGACTGGCTCACGAGAGAAGGCGGCGAGCTGCCC 2820
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2761 GCCATGGGCTCCGTGAAGCCCGCCCTGGACTGGCTCACGAGAGAAGGCGGCGAGCTGCCC 2820

Qy       2821 GAGGCGGACGAGTGGACGGGGGGTGACGCACCCGCCTTCTCCACTTCCACCCTCCTCTCA 2880
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2821 GAGGCGGACGAGTGGACGGGGGGTGACGCACCCGCCTTCTCCACTTCCACCCTCCTCTCA 2880

Qy       2881 GGTGATGGAGACTCAGCAGAGCTTGAGGGCCCTCCCGCCCCCCTCATCCTCCCGTCCAGC 2940
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2881 GGTGATGGAGACTCAGCAGAGCTTGAGGGCCCTCCCGCCCCCCTCATCCTCCCGTCCAGC 2940

Qy       2941 CTCGACTACCAGTATGACACCCCCGGGCTCTGGGAGCTGGAAGAGGCGACCTTGGGGGCA 3000
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2941 CTCGACTACCAGTATGACACCCCCGGGCTCTGGGAGCTGGAAGAGGCGACCTTGGGGGCA 3000

Qy       3001 AGCTCCTGCCCCCTGTGTGGAGAGCGTTCAGGGCTCCACGTTGATGCCGGTCCATGTGGAG 3060
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3001 AGCTCCTGCCCCCTGTGTGGAGAGCGTTCAGGGCTCCACGTTGATGCCGGTCCATGTGGAG 3060

Qy       3061 CGGGAAATCCGGCTGCTAGGCAGGAACCTGCACCTTTTCCAGGATGGCCCAGGAGACAAT 3120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3061 CGGGAAATCCGGCTGCTAGGCAGGAACCTGCACCTTTTCCAGGATGGCCCAGGAGACAAT 3120

Qy       3121 GAGTGTGTGATGGAGCTGGAGGGCCTCGAGGTGGTGGTTGAGGCCCGGGTCGAGTGTGAG 3180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       3121 GAGTGTGTGATGGAGCTGGAGGGCCTCGAGGTGGTGGTTGAGGCCCGGGTCGAGTGTGAG 3180

Qy       3181 CCACCTCCAGATACCCAGTGCCATGTCACCTGCCAGCAGCACCAGCTCAGCTATGAGGCT 3240
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3181 CCACCTCCAGATACCCAGTGCCATGTCACCTGCCAGCAGCACCAGCTCAGCTATGAGGCT 3240

Qy       3241 CTGCAGCCGGAGCTCCGTGTGGGGCTGTTTCTGCGTCGGGCCGGCCGTCTGCGTGTGGAC 3300
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3241 CTGCAGCCGGAGCTCCGTGTGGGGCTGTTTCTGCGTCGGGCCGGCCGTCTGCGTGTGGAC 3300

Qy       3301 AGTGCTGAGGGGCTGCATGTGGTACTGTATGACTGTTCCGTGGGACATGGAGACTGCAGC 3360
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3301 AGTGCTGAGGGGCTGCATGTGGTACTGTATGACTGTTCCGTGGGACATGGAGACTGCAGC 3360

Qy       3361 CGCTGCCAAACTGCCATGCCCCAGTATGGCTGTGTGTGGTGTGAGGGGGAGCGTCCACGT 3420
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3361 CGCTGCCAAACTGCCATGCCCCAGTATGGCTGTGTGTGGTGTGAGGGGGAGCGTCCACGT 3420

Qy       3421 TGTGTGACCCGGGAGGCCTGTGGTGAGGCTGAGGCTGTGGCCACCCAGTGCCCAGCGCCC 3480
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3421 TGTGTGACCCGGGAGGCCTGTGGTGAGGCTGAGGCTGTGGCCACCCAGTGCCCAGCGCCC 3480

Qy       3481 CTCATCCACTCGGTGGAGCCACTGACTGGGCCTGTAGACGGAGGCACCCGTGTCACCATC 3540
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3481 CTCATCCACTCGGTGGAGCCACTGACTGGGCCTGTAGACGGAGGCACCCGTGTCACCATC 3540

Qy       3541 AGGGGCTCCAACCTGGGCCAGCATGTGCAGGATGTGCTGGGCATGGTCACGGTGGCTGGA 3600
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3541 AGGGGCTCCAACCTGGGCCAGCATGTGCAGGATGTGCTGGGCATGGTCACGGTGGCTGGA 3600

Qy       3601 GTGCCCTGTGCTGTGGATGCCCAGGAGTACGAGGTCTCCAGCAGCCTCGTGTGCATCACC 3660
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3601 GTGCCCTGTGCTGTGGATGCCCAGGAGTACGAGGTCTCCAGCAGCCTCGTGTGCATCACC 3660

Qy       3661 GGGGCCAGTGGGGAGGAGGTGGCCGGCGCCACAGCGGTGGAGGTGCCGGGAAGAGGACGT 3720
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3661 GGGGCCAGTGGGGAGGAGGTGGCCGGCGCCACAGCGGTGGAGGTGCCGGGAAGAGGACGT 3720

Qy       3721 GGTGTCTCAGAACACGACTTTGCCTACCAGGATCCGAAGGTCCATTCCATCTTCCCGGCC 3780
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3721 GGTGTCTCAGAACACGACTTTGCCTACCAGGATCCGAAGGTCCATTCCATCTTCCCGGCC 3780

Qy       3781 CGCGGCCCCAGAGCTGGGGGCACCCGTCTCACCCTGAATGGCTCCAAGCTCCTGACTGGG 3840
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3781 CGCGGCCCCAGAGCTGGGGGCACCCGTCTCACCCTGAATGGCTCCAAGCTCCTGACTGGG 3840

Qy       3841 CGGCTGGAGGACATCCGAGTGGTGGTTGGAGACCAGCCTTGTCACTTGCTGCCGGAGCAG 3900
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3841 CGGCTGGAGGACATCCGAGTGGTGGTTGGAGACCAGCCTTGTCACTTGCTGCCGGAGCAG 3900

Qy       3901 CAGTCAGAACAACTGCGGTGTGAGACCAGCCCACGCCCCACGCCTGCCACGCTCCCTGTG 3960
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3901 CAGTCAGAACAACTGCGGTGTGAGACCAGCCCACGCCCCACGCCTGCCACGCTCCCTGTG 3960

Qy       3961 GCTGTGTGGTTTGGGGCCACGGAGCGGAGGCTTCAACGCGGACAGTTCAAGTATACCTTG 4020
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3961 GCTGTGTGGTTTGGGGCCACGGAGCGGAGGCTTCAACGCGGACAGTTCAAGTATACCTTG 4020

Qy       4021 GACCCCAACATCACCTCTGCTGGCCCCACCAAGAGCTTCCTCAGTGGAGGACGTGAGATA 4080
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       4021 GACCCCAACATCACCTCTGCTGGCCCCACCAAGAGCTTCCTCAGTGGAGGACGTGAGATA 4080

Qy       4081 TGCGTCCGTGGCCAGAATCTGGACGTGGTACAGACGCCAAGAATCCGGGTGACCGTGGTC 4140
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4081 TGCGTCCGTGGCCAGAATCTGGACGTGGTACAGACGCCAAGAATCCGGGTGACCGTGGTC 4140

Qy       4141 TCGAGAATGCTGCAGCCCAGCCAGGGGCTTGGACGGAGGCGTCGCGTGGTCCCGGAGACG 4200
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4141 TCGAGAATGCTGCAGCCCAGCCAGGGGCTTGGACGGAGGCGTCGCGTGGTCCCGGAGACG 4200

Qy       4201 GCATGTTCCCTTGGACCCTCCTGCAGTAGCCAGCAATTTGAGGAGCCGTGCCATGTCAAC 4260
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4201 GCATGTTCCCTTGGACCCTCCTGCAGTAGCCAGCAATTTGAGGAGCCGTGCCATGTCAAC 4260

Qy       4261 TCCTCCCAGCTCATCACGTGCCGCACACCTGCCCTCCCAGGCCTGCCTGAGGACCCCTGG 4320
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4261 TCCTCCCAGCTCATCACGTGCCGCACACCTGCCCTCCCAGGCCTGCCTGAGGACCCCTGG 4320

Qy       4321 GTCCGGGTGGAATTTATCCTTGACAACCTGGTCTTTGACTTTGCAACACTGAACCCCACA 4380
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4321 GTCCGGGTGGAATTTATCCTTGACAACCTGGTCTTTGACTTTGCAACACTGAACCCCACA 4380

Qy       4381 CCTTTCTCCTATGAGGCCGACCCCACCCTGCAGCCACTCAACCCTGAGGACCCCACCATG 4440
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4381 CCTTTCTCCTATGAGGCCGACCCCACCCTGCAGCCACTCAACCCTGAGGACCCCACCATG 4440

Qy       4441 CCATTCCGGCACAAGCCTGGGAGTGTGTTCTCCGTGGAGGGGGAGAACCTGGACCTTGCA 4500
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4441 CCATTCCGGCACAAGCCTGGGAGTGTGTTCTCCGTGGAGGGGGAGAACCTGGACCTTGCA 4500

Qy       4501 ATGTCCAAGGAGGAGGTGGTGGCTATGATAGGGGATGGCCCCTGTGTGGTGAAGACGCTG 4560
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4501 ATGTCCAAGGAGGAGGTGGTGGCTATGATAGGGGATGGCCCCTGTGTGGTGAAGACGCTG 4560

Qy       4561 ACGCGGCACCACCTGTACTGCGAGCCCCCCGTGGAGCAGCCCCTGCCACGGCACCATGCC 4620
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4561 ACGCGGCACCACCTGTACTGCGAGCCCCCCGTGGAGCAGCCCCTGCCACGGCACCATGCC 4620

Qy       4621 CTCCGAGAGGCACCTGACTCTTTGCCTGAGTTCACGGTGCAGATGGGGAACTTGCGCTTC 4680
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4621 CTCCGAGAGGCACCTGACTCTTTGCCTGAGTTCACGGTGCAGATGGGGAACTTGCGCTTC 4680

Qy       4681 TCCCTGGGTCACGTGCAGTATGACGGCGAGAGCCCTGGGGCTTTTCCTGTGGCAGCCCAG 4740
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4681 TCCCTGGGTCACGTGCAGTATGACGGCGAGAGCCCTGGGGCTTTTCCTGTGGCAGCCCAG 4740

Qy       4741 GTGGGCTTGGGGGTGGGCACCTCTCTTCTGGCTCTGGGTGTCATCATCATTGTCCTCATG 4800
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4741 GTGGGCTTGGGGGTGGGCACCTCTCTTCTGGCTCTGGGTGTCATCATCATTGTCCTCATG 4800

Qy       4801 TACAGGAGGAAGAGCAAGCAGGCCCTGAGGGACTATAAGAAGGTTCAGATCCAGCTGGAG 4860
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4801 TACAGGAGGAAGAGCAAGCAGGCCCTGAGGGACTATAAGAAGGTTCAGATCCAGCTGGAG 4860

Qy       4861 AATCTGGAGAGCAGTGTGCGGGACCGCTGCAAGAAGGAATTCACAGACCTCATGACTGAG 4920
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4861 AATCTGGAGAGCAGTGTGCGGGACCGCTGCAAGAAGGAATTCACAGACCTCATGACTGAG 4920

Qy       4921 ATGACCGATCTCACCAGTGACCTCCTGGGCAGCGGCATCCCCTTCCTCGACTACAAGGTG 4980
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       4921 ATGACCGATCTCACCAGTGACCTCCTGGGCAGCGGCATCCCCTTCCTCGACTACAAGGTG 4980

Qy       4981 TATGCGGAGAGGATCTTCTTCCCTGGGCACCGCGAGTCGCCCTTGCACCGGGACCTGGGT 5040
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4981 TATGCGGAGAGGATCTTCTTCCCTGGGCACCGCGAGTCGCCCTTGCACCGGGACCTGGGT 5040

Qy       5041 GTGCCTGAGAGCAGACGGCCCACTGTGGAGCAAGGGCTGGGGCAGCTCTCTAACCTGCTC 5100
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5041 GTGCCTGAGAGCAGACGGCCCACTGTGGAGCAAGGGCTGGGGCAGCTCTCTAACCTGCTC 5100

Qy       5101 AACAGCAAGCTCTTCCTCACCAAGTTCATCCACACGCTGGAGAGCCAGCGCACCTTTTCA 5160
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5101 AACAGCAAGCTCTTCCTCACCAAGTTCATCCACACGCTGGAGAGCCAGCGCACCTTTTCA 5160

Qy       5161 GCTCGGGACCGTGCCTACGTGGCATCTCTGCTCACCGTGGCACTGCATGGGAAGCTTGAG 5220
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5161 GCTCGGGACCGTGCCTACGTGGCATCTCTGCTCACCGTGGCACTGCATGGGAAGCTTGAG 5220

Qy       5221 TATTTCACTGACATCCTCCGCACTCTGCTCAGTGACCTGGTTGCCCAGTATGTGGCCAAG 5280
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5221 TATTTCACTGACATCCTCCGCACTCTGCTCAGTGACCTGGTTGCCCAGTATGTGGCCAAG 5280

Qy       5281 AACCCCAAGCTGATGCTGCGCAGGACAGAGACTGTGGTGGAGAAGCTGCTCACCAACTGG 5340
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5281 AACCCCAAGCTGATGCTGCGCAGGACAGAGACTGTGGTGGAGAAGCTGCTCACCAACTGG 5340

Qy       5341 ATGTCCATCTGTCTGTATACCTTCGTGAGGGACTCCGTAGGGGAGCCTCTGTACATGCTC 5400
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5341 ATGTCCATCTGTCTGTATACCTTCGTGAGGGACTCCGTAGGGGAGCCTCTGTACATGCTC 5400

Qy       5401 TTTCGAGGGATTAAGCACCAAGTGGATAAGGGGCCAGTGGACAGTGTGACAGGCAAGGCC 5460
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5401 TTTCGAGGGATTAAGCACCAAGTGGATAAGGGGCCAGTGGACAGTGTGACAGGCAAGGCC 5460

Qy       5461 AAATACACCTTGAACGACAACCGCCTGCTCAGAGAGGATGTGGAGTACCGTCCCCTGACC 5520
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5461 AAATACACCTTGAACGACAACCGCCTGCTCAGAGAGGATGTGGAGTACCGTCCCCTGACC 5520

Qy       5521 TTGAATGCACTATTGGCTGTGGGGCCTGGGGCAGGAGAGGCCCAGGGCGTGCCCGTGAAG 5580
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5521 TTGAATGCACTATTGGCTGTGGGGCCTGGGGCAGGAGAGGCCCAGGGCGTGCCCGTGAAG 5580

Qy       5581 GTCCTAGACTGTGACACCATCTCCCAGGCAAAGGAGAAGATGCTGGACCAGCTTTATAAA 5640
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5581 GTCCTAGACTGTGACACCATCTCCCAGGCAAAGGAGAAGATGCTGGACCAGCTTTATAAA 5640

Qy       5641 GGAGTGCCTCTCACCCAGCGGCCAGACCCTCGCACCCTTGATGTTGAGTGGCGGTCTGGG 5700
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5641 GGAGTGCCTCTCACCCAGCGGCCAGACCCTCGCACCCTTGATGTTGAGTGGCGGTCTGGG 5700

Qy       5701 GTGGCCGGGCACCTCATTCTTTCTGACGAGGATGTCACTTCTGAGGTCCAGGGTCTGTGG 5760
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5701 GTGGCCGGGCACCTCATTCTTTCTGACGAGGATGTCACTTCTGAGGTCCAGGGTCTGTGG 5760

Qy       5761 AGGCGCCTGAACACACTGCAGCATTACAAGGTCCCAGATGGAGCAACTGTGGCCCTCGTC 5820
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5761 AGGCGCCTGAACACACTGCAGCATTACAAGGTCCCAGATGGAGCAACTGTGGCCCTCGTC 5820

Qy       5821 CCCTGCCTCACCAAGCATGTGCTCCGGGAAAACCAGGATTATGTCCCTGGAGAGCGGACC 5880
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       5821 CCCTGCCTCACCAAGCATGTGCTCCGGGAAAACCAGGATTATGTCCCTGGAGAGCGGACC 5880

Qy       5881 CCAATGCTGGAGGATGTAGATGAGGGGGGCATCCGGCCCTGGCACCTGGTGAAGCCAAGT 5940
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5881 CCAATGCTGGAGGATGTAGATGAGGGGGGCATCCGGCCCTGGCACCTGGTGAAGCCAAGT 5940

Qy       5941 GATGAGCCGGAGCCGCCCAGGCCTCGGAGGGGCAGCCTTCGGGGCGGGGAGCGTGAGCGC 6000
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5941 GATGAGCCGGAGCCGCCCAGGCCTCGGAGGGGCAGCCTTCGGGGCGGGGAGCGTGAGCGC 6000

Qy       6001 GCCAAGGCCATCCCTGAGATCTACCTGACCCGCCTGCTGTCCATGAAGGGCACCCTGCAG 6060
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6001 GCCAAGGCCATCCCTGAGATCTACCTGACCCGCCTGCTGTCCATGAAGGGCACCCTGCAG 6060

Qy       6061 AAGTTCGTGGATGACCTGTTCCAGGTGATTCTCAGCACCAGCCGCCCCGTGCCGCTCGCT 6120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6061 AAGTTCGTGGATGACCTGTTCCAGGTGATTCTCAGCACCAGCCGCCCCGTGCCGCTCGCT 6120

Qy       6121 GTGAAGTACTTCTTTGACCTGCTGGATGAGCAGGCCCAGCAGCATGGCATCTCCGACCAG 6180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6121 GTGAAGTACTTCTTTGACCTGCTGGATGAGCAGGCCCAGCAGCATGGCATCTCCGACCAG 6180

Qy       6181 GACACCATCCACATCTGGAAGACCAACAGCTTGCCTCTGAGGTTCTGGATCAATATAATA 6240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6181 GACACCATCCACATCTGGAAGACCAACAGCTTGCCTCTGAGGTTCTGGATCAATATAATA 6240

Qy       6241 AAAAACCCGCAGTTTGTGTTCGACGTGCAAACATCTGATAACATGGATGCGGTGCTCCTT 6300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6241 AAAAACCCGCAGTTTGTGTTCGACGTGCAAACATCTGATAACATGGATGCGGTGCTCCTT 6300

Qy       6301 GTCATTGCACAGACCTTCATGGACGCCTGCACCCTGGCCGACCACAAGCTGGGCCGGGAC 6360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6301 GTCATTGCACAGACCTTCATGGACGCCTGCACCCTGGCCGACCACAAGCTGGGCCGGGAC 6360

Qy       6361 TCCCCGATCAACAAACTTCTGTATGCACGGGACATTCCCCGGTACAAGCGGATGGTGGAA 6420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6361 TCCCCGATCAACAAACTTCTGTATGCACGGGACATTCCCCGGTACAAGCGGATGGTGGAA 6420

Qy       6421 AGGTACTATGCAGACATCAGACAGACTGTCCCAGCCAGCGACCAAGAGATGAACTCTGTC 6480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6421 AGGTACTATGCAGACATCAGACAGACTGTCCCAGCCAGCGACCAAGAGATGAACTCTGTC 6480

Qy       6481 CTGGCTGAACTGTCCTGGAACTACTCCGGAGACCTCGGGGCGCGAGTGGCCCTGCATGAA 6540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6481 CTGGCTGAACTGTCCTGGAACTACTCCGGAGACCTCGGGGCGCGAGTGGCCCTGCATGAA 6540

Qy       6541 CTCTACAAGTACATCAACAAGTACTATGACCAGATCATCACTGCCCTGGAGGAGGATGGC 6600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6541 CTCTACAAGTACATCAACAAGTACTATGACCAGATCATCACTGCCCTGGAGGAGGATGGC 6600

Qy       6601 ACGGCCCAGAAGATGCAGCTGGGCTATCGGCTCCAGCAGATTGCAGCTGCTGTGGAAAAC 6660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6601 ACGGCCCAGAAGATGCAGCTGGGCTATCGGCTCCAGCAGATTGCAGCTGCTGTGGAAAAC 6660

Qy       6661 AAGGTCACAGATCTATAGGAACCCAGGAGCCACGGCCTGCTGTTGCTTCAGCCTGGCCTG 6720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6661 AAGGTCACAGATCTATAGGAACCCAGGAGCCACGGCCTGCTGTTGCTTCAGCCTGGCCTG 6720

Qy       6721 GGCAGCCCTGGAAGCTCGGAGGAGAGGCCACCTTCTTAGGTGCCTGTAGTGACTGACAAG 6780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       6721 GGCAGCCCTGGAAGCTCGGAGGAGAGGCCACCTTCTTAGGTGCCTGTAGTGACTGACAAG 6780

Qy       6781 CAGAGTTAGTGGAAGGTGACTCCCAGTCTCCTGGTGGCTCTGGCCTCGGCCCTGCTGGAT 6840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6781 CAGAGTTAGTGGAAGGTGACTCCCAGTCTCCTGGTGGCTCTGGCCTCGGCCCTGCTGGAT 6840

Qy       6841 CCACCTCCTAGACCCGGGGCCTCAAGGCTCATGGGGTAGTACCCAGCCTGCTCCCCGAGT 6900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6841 CCACCTCCTAGACCCGGGGCCTCAAGGCTCATGGGGTAGTACCCAGCCTGCTCCCCGAGT 6900

Qy       6901 CCAGCGACCCTGTGACACCGGTCTGCAGGGAGTTGGGGACTAAGGGCTTCCAGAGAGTGG 6960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6901 CCAGCGACCCTGTGACACCGGTCTGCAGGGAGTTGGGGACTAAGGGCTTCCAGAGAGTGG 6960

Qy       6961 CTGGAAGAGACTCCAGGCCCCTGGGGAGACTGTACTGTTCCTGAACACTGGCCTTGGCCA 7020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6961 CTGGAAGAGACTCCAGGCCCCTGGGGAGACTGTACTGTTCCTGAACACTGGCCTTGGCCA 7020

Qy       7021 CACTGGGATTCGGAGAGGAAGGAGGAGAGCCCCATGCTTCCTGTCTGCCTCCTCCACCAT 7080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       7021 CACTGGGATTCGGAGAGGAAGGAGGAGAGCCCCATGCTTCCTGTCTGCCTCCTCCACCAT 7080

Qy       7081 CCCTGACCTCAGTTGAGCTGCCTCTGGCCTTGTTGCTGCTGCCACATCCTAGGTCTAAGA 7140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       7081 CCCTGACCTCAGTTGAGCTGCCTCTGGCCTTGTTGCTGCTGCCACATCCTAGGTCTAAGA 7140

Qy       7141 GTTGAACGCCTCTCCTAGGCCACTACAAACTGACCCCTCAGCAGGGCTGGCTGCCACAGG 7200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       7141 GTTGAACGCCTCTCCTAGGCCACTACAAACTGACCCCTCAGCAGGGCTGGCTGCCACAGG 7200

Qy       7201 GCTGCCCTGCCTCATAGGTAGCCATGGTGAGGGCTATCTGCTGCAGGGGGGTCTTGGGGA 7260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       7201 GCTGCCCTGCCTCATAGGTAGCCATGGTGAGGGCTATCTGCTGCAGGGGGGTCTTGGGGA 7260

Qy       7261 GAGTGGTGACTCCATTGACCCAGCTTTTCATTAAAGGATAACACACTG 7308
              ||||||||||||||||||||||||||||||||||||||||||||||||
Db       7261 GAGTGGTGACTCCATTGACCCAGCTTTTCATTAAAGGATAACACACTG 7308
```

Appendix 2

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AFS94677
ID   AFS94677 standard; DNA; 5412 BP.
XX
AC   AFS94677;
XX
DT   20-SEP-2007  (first entry)
XX
DE   Human transcript sequence, SEQ ID 14076.
XX
KW   DNA detection; RNA detection; exon; ds.
XX
OS   Homo sapiens.
XX
PN   WO200268579-A2.
XX
PD   06-SEP-2002.
XX
PF   10-JAN-2002; 2002WO-US000284.
XX
PR   10-JAN-2001; 2001US-00756696.
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XX
PA   (PEKE ) PE CORP NY.
XX
PI   Venter CJ,  Adams M,  Li PWD,  Myers EW;
XX
DR   WPI; 2002-682812/73.
XX
PT   New isolated nucleic acid detection reagent for detecting the presence of
PT   specified human exons.
XX
PS   Claim 4; SEQ ID NO 14076; 40pp; English.
XX
CC   The present invention relates to a novel isolated nucleic acid detection
CC   reagent for detecting the presence of specified human exons. The exon
CC   sequences cover every identified human transcript and exon comprising
CC   every gene/coding region of the human genome. The present sequence is one
CC   such exon sequence. The nucleic acid detection agent is used for
CC   detecting the presence of at least 100000, at least 2000, at least 50000
CC   or at least 10000 human exons. The sequences that span exon-exon
CC   junctions eliminate false signals caused by genomic contamination. This
CC   is because a detection element comprising two neighboring exons as one
CC   contiguous sequence will not hybridize to genomic DNA comprising
CC   intervening intronic DNA. These detection elements will only hybridize to
CC   expressed mRNA transcripts in which the exons are connected and the
CC   intronic sequence has been removed, therefore forming one contiguous
CC   stretch of sequence corresponding to the sequence of the detection
CC   element that spans the exon-exon junction.
XX
SQ   Sequence 5412 BP; 945 A; 1831 C; 1688 G; 948 T; 0 U; 0 Other;

  Query Match             12.8%;  Score 935.2;  DB 1;  Length 5412;
  Best Local Similarity   57.8%;  Pred. No. 4.7e-188;
  Matches 2102;  Conservative    0;  Mismatches 1243;  Indels  291;  Gaps   13;

Qy       3200 GCCATGTCACCTGCCAGCAGCACCAGCTCAGCTATGAGGCTCTGCAGCCGGAGCTCCGTG 3259
              |||   ||  |||||||   |||||| |                  |||| ||||||||  |
Db       1907 GCCTCATCCACTGCCAGGCCCACCAGTTTTATCCCTCCATGTCCCAGCGGGAGCTCCCAG 1966

Qy       3260 TGGGGCTGTTTCTGCGTCGGGCCGGCCGTCTGCGTGTGGACAGTGCTGAGGGGCTGCATG 3319
              ||   | |   |     | ||  |      | | |  ||||||    |  |  | ||  |||
Db       1967 TGCCCATCTACGTCACCCAGGGTGAAGCCCAGAGGCTGGACAACACCCATGCTCTTTATG 2026

Qy       3320 TGGTACTGTATGACTGTTCCGTGGGACATGGAGACTGCAGCCGCTGCCAAACTGCCATGC 3379
              || | ||||| |||||   || |||| ||     |||||||||| ||||||| | ||||
Db       2027 TGATCCTGTACGACTGCGCCATGGGCCACCCGGACTGCAGCCACTGCCAAGCGGCCAACA 2086

Qy       3380 CCCAGTATGGCTGTGTGTGGTGTGAGGGGGAGCGTCCACGTTGTGTGACCCGGGAGGCCT 3439
                           |||||  |||||||||  |   |   |   ||     |||      |    | | |||
Db       2087 GGAGCCTGGGCTGCCTGTGGTGTGCTGACGGCCAGCCTGCCTGT---CGCTATGGGCCCT 2143

Qy       3440 GTGGTGAGGCTGAGGCTGTGGCCACCCAGTGCCCAGCGCCCCTCATCCACTCGGTGGAGC 3499
                 |    | | | ||||||||      | |||  || ||||||  |||  |   | || ||||
Db       2144 TGTGCCCGCCGGGGGCTGTGGAGCTGCTGTGTCCTGCGCCCAGCATTGATGCAGTCGAGC 2203

Qy       3500 CACTGACTGGGCCTGTAGACGGAGGCACCCGTGTCACCATCAGGGGCTCCAACCTGGGCC 3559
              | ||||| || ||     || ||||||        ||||||||  |||||||||||||||
Db       2204 CCCTGACCGGTCCCCCTGAGGGAGGCTTGGCCCTCACCATCCTGGGCTCCAACCTGGGCC 2263

Qy       3560 AGCATGTGCAGGATGTGCTGGGCATGGTCACGGTGGCTGGAGTGCCCTGTGCTGTGGATG 3619
                |    |      ||||||| |   |     || |   |||||   |     ||||||        ||
Db       2264 GGGCCTTCGCCGATGTGCAGTACGCCGTGAGCGTGGCCAGCCGGCCCTGCAACCCTGAGC 2323

Qy       3620 CCCAGGAGTACGAGGTCTCCAGCAGCCTCGTGTGCATCACCGGGGCCAGTGGGGAGGAGG 3679
              ||        |||        ||     |   |    |  |||||    | ||       |           | |
Db       2324 CCTCTCTCTACCGCACGTCGGCCCGGATTGTGTGTGTGACATCTCCTGCCCCCAATGGCA 2383

Qy       3680 TGGCCGGCGCCACAGCGGTGGAGGTGCCGGGAAGAGGACGTGGTGTCTCAGAACACGACT 3739
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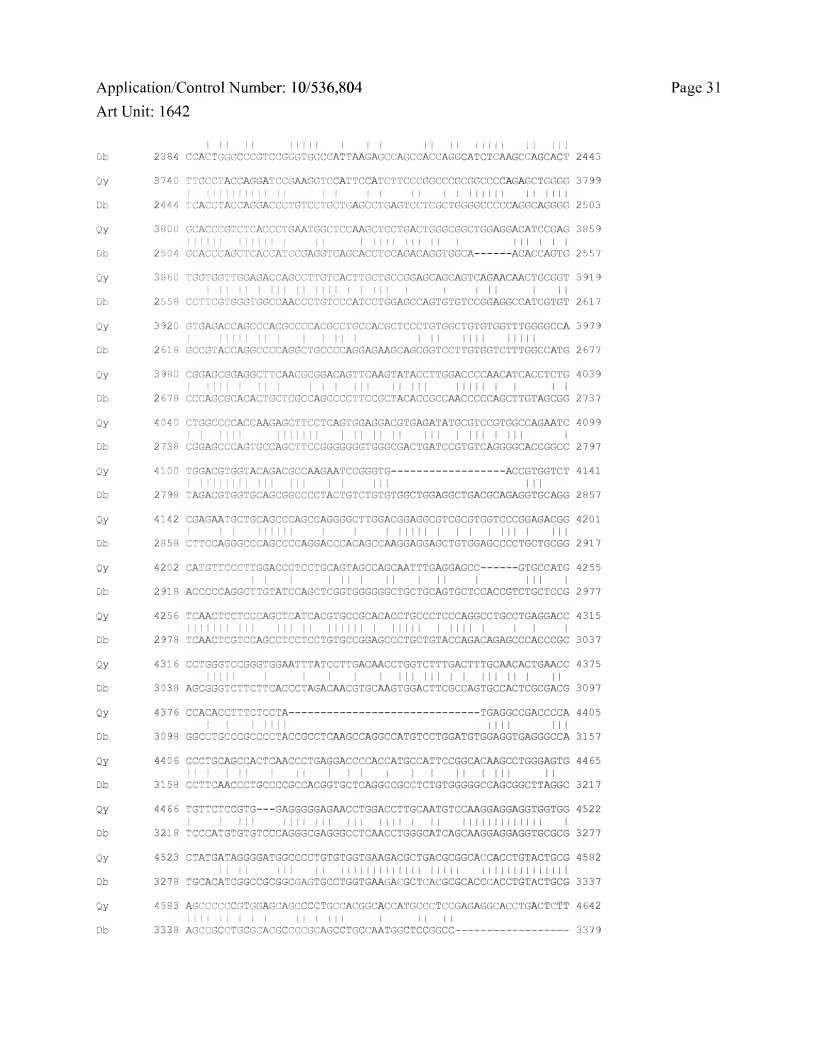

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Qy       4703 ACGGCGAGACCCTCGG---GCTTTTCCTGTGGCAGCCCAGGTGGGCTTGGGGGTGGGCA 4759
Db       3440 AGGCTGAACCCCCGGTGTCTGCCTTTCCCGTGGAGGCCCAGGCAGGCGTGGGCATGGGTG 3499

Qy       4760 CCTCTCTTCTGGCTCTGGGTGTCATCATCATTGTCCTCATGTACAGGAGGAAGAGCAAGC 4819
Db       3500 CTGCAGTGCTGATTGCCGCCGTGCTCCTCCTCACCCTCATGTACAGGCACAAGAGCAAGC 3559

Qy       4820 AGGCCCTGAGGGACTATAAGAAGGTTCAGATCCAGCTGGAGAATCTGGAGAACGAGTGTGC 4879
Db       3560 AGGCCCTGCGGGACTACCAGAAGGTGCTAGTGCAGCTGGAGAGCCTGGAGAACCGGCGTGG 3619

Qy       4880 GGGACCGCGTGCAAGAAGGAATTCACAGACCTCATGACTGAGATGACCGATCTCACCAGTG 4939
Db       3620 GAGACCAGTGCCGCAAGGAGTTCACAGACCTCATGACGGAGATGACCGACCTCAGCAGCG 3679

Qy       4940 ACCTCCTGGGCAGCGGCATCCCCTTCCTCGACTACAAGGTGTATGCGGAGAGGATCTTCT 4999
Db       3680 ACCTGGAGGGCAGCGGGATCCCCTTCCTGGACTACCGCACCTACGCCGAGCGCGCCTTCT 3739

Qy       5000 TCCCTGGGCACCGCGAGTCGCCCTTGCACCGGGACCTGGGTGTGCC------TGAGAGCA 5053
Db       3740 TCCCTGGCCATGGCGGTTGCCCGCTGCAGCCCAAGCCTGAGGGGCCAGGGAGGACGGCC 3799

Qy       5054 GACGGCCCACTGTGGAGCAAGGGCTGGGGCAGCTCTCTAACCTGCTCAACAGCAAGCTCT 5113
Db       3800 ACTGTGCCACTGTGGCCAGGGCCTCACGCAGCTCTCCAACCTGCTCAACAGCAAGCTCT 3859

Qy       5114 TCCTC---------------------------------------------------------- 5118
Db       3860 TCCTCCTCACGGTGAGGGCCGTGTGGCGGGAGTGCCCAGTGGGCAAGGAGGTGGGGCTGG 3919

Qy       5119 ------------------ACCAAGTTCATCCACACGCTGGAGAGCCAGCGCACCTTTTCAG 5161
Db       3920 GGAACTACTGGCCTGAGACAAAGCTCATCCACACCCTGGAGGAGCAGCCCAGCTTTTCCC 3979

Qy       5162 CTCGGGACCGTCGTCACGTGGCATCTCTGCTCACCGTGGCACTGCATGGGAAGCTTGAGT 5221
Db       3980 AGAGGGATCGCTGCCATGTGGCTTCGCTGCTGTCGCTAGCGCTACACGGCAAGCTGGAGT 4039

Qy       5222 ATTTCACTGACATCCTCCGCACTCTGCTCAGTGACCTGGTTGCCCAGTATGTGGCCAAGA 5281
Db       4040 ACCTGACGGACATCATGAGGACCCTGCTGGGTGACCTGGCGGCCCATTACGTGCACAGGA 4099

Qy       5282 ACCCCAAGCTGATGCTGCGCAGGACAGAGACTGTGGTGGAGAAGCTGCTCACCAACTGGA 5341
Db       4100 ACCCCAAGCTCATGCTACGCAGGACAGAGACCATGGTGGAGAAACTGCTCACCAACTGGC 4159

Qy       5342 TGTCCATCTGTCTGTATACCTTCGTGAGGGACTCCGTAGGGGAGCCTCTGTACATGCTCT 5401
Db       4160 TGTCCATCTGCCTGTACGCCTTCCTGAGGGAGGTGGCTGGTGAACCACTGTACATGCTCT 4219

Qy       5402 TTCGAGGGATTAAGCACCAAGTGGATAAGGGGCCAGTGGACAGTGTGACAGGCAAGGCCA 5461
Db       4220 TCCGGGCCATCCAGTACCAGGTGGACAAAGGCCCCGTGGACGCCGTGACAGGCAAGGCCA 4279

Qy       5462 AATACACCTTGAACGACAACCGCCTGCTCAGAGAGGATGTGGAGTACCGTCCCCTGACCT 5521
Db       4280 AACGGACCCTGAATGATAGCCGCTTGCTGCGGGAGGACGTGGAGTTCCAGCCCCTGACGC 4339

Qy       5522 TGAATGCACTATTGGCTGTGGGGCCTGGGGCAG------------GAGAGGCCCAGGGCG 5569
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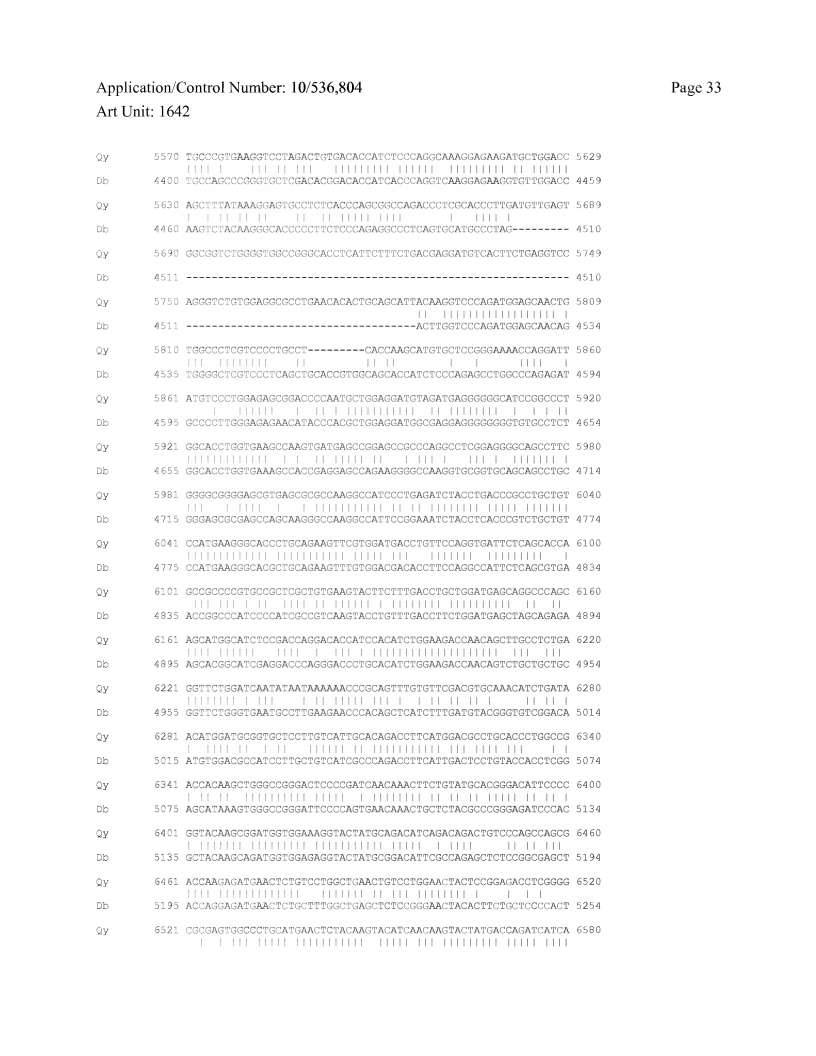

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                |||||||||||||||      || ||||||| ||||||||| ||  || || ||||||
Db        5315 GTGCCCTGGAGGAGGACCCTGTGGGCCAGAAGCTGCAGCTGGCCTGCCGCCTGCAGCAGG 5374

Qy        6641 TTGCAGCTGCTGTGGAAAACAAGGTCACAGATCTAT 6676
               | || ||    ||||||||||| || || || || |
Db        5375 TCGCCGCCCTGGTGGAAAACAAAGTGACTGACCTGT 5410
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